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# Pharmacokinetics of Single Dose Lidocaine and Epinephrine Following Iontophoresis of the Tympanic Membrane in a Double-Blinded Randomized Trial

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**Objective:** To evaluate local and systemic safety of bilateral iontophoretic administration of lidocaine with epinephrine or lidocaine alone to the tympanic membrane (TM).

**Study Design:** A randomized, double-blind, two-arm study was conducted at a single center. Healthy adults were randomized to bilateral iontophoretic treatment with 2% lidocaine, 1:100,000 epinephrine, or 2% lidocaine (control). Otoscopy, cranial nerve examination, tympanometry, and audiometry safety evaluations were conducted before and 3-days post-procedure. Systemic safety was evaluated via analysis of vital signs taken before and up to 120 minutes post-iontophoresis, and blood samples collected before and up to 230 minutes post-iontophoresis.

**Results:** Twenty-five subjects were treated with bilateral iontophoresis of either lidocaine and epinephrine (n = 15 subjects) or lidocaine alone (n = 10). Mean plasma epinephrine concentrations for both groups remained within the normal range for endogenous epinephrine. Mean plasma concentrations of lidocaine were not statistically different

between groups, ranging from 0.245 to 2.28 ng/ml after administration of lidocaine with epinephrine (immediate post-iontophoresis to 230 min post-iontophoresis), compared with 1.35 to 2.14 ng/ml after administration of lidocaine alone. The presence of epinephrine slowed the systemic absorption of lidocaine. Lidocaine levels ( $C_{max}$  2.24 ng/ml) were approximately 2000-fold lower than the threshold for minor lidocaine toxicity. No device-, procedure- or drug-related adverse events were reported.

**Conclusion:** The local and systemic safety of bilateral iontophoretic delivery of 2% lidocaine, 1:100,000 epinephrine to the TM was demonstrated by low plasma levels of drug and absence of both serious and non-serious device-, procedure-, or drug-related adverse events.

**Key Words:** Epinephrine—Iontophoresis—Lidocaine—Local anesthesia—Pharmacokinetics—Topical anesthesia.

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Otitis Media (middle ear inflammation) is an extremely common disease of childhood, with a reported 75% of children in the United States experiencing at least one episode by age 3 (1). When conservative treatment fails and disease persists, tympanostomy surgery is

performed to place a ventilating tube across the tympanic membrane (TM). Tympanostomy procedures are very common, with a reported 700,000 pediatric tympanostomy procedures in the United States annually (2). Although usually considered surgically straightforward, general anesthesia in an operating-room setting is required to perform the procedure in young children to address pain, anxiety, and movement, whereas in older children and adults the procedure can be performed using local anesthesia in an office setting.

Clinical usage of otic iontophoresis systems have been reported and provided preliminary data on safety (cochlear responses and side effects) of iontophoretic administration of lidocaine and epinephrine to the tympanic membrane, however none reported on systemic exposure resulting from iontophoretic drug delivery. Historically, there have been no Food and Drug Administration (FDA)-approved or practical (e.g., tolerable, efficient) local anesthetics suitable for use in young children in an office setting. A novel otic 2% lidocaine

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and 1:100,000 epinephrine local anesthetic and iontophoretic drug-delivery system was developed for use in young children, enabling tympanostomy tube placement in an office setting, and obviating the need for general anesthesia. Given the vulnerable target population and target tissue, safety of the iontophoretic administration is critical, and the technology development and safety program included evaluation of local and systemic safety using validated, highly sensitive state-of-the-art methods, for the specific drug formulation and system as described in this report. The objective of this study was to evaluate local and systemic safety of bilateral iontophoretic administration of 2% lidocaine, 1:100,000 epinephrine, or 2% lidocaine alone (as a control) to the tympanic membrane.

## MATERIALS AND METHODS

### Study Design and Oversight

This was a randomized, double-blind (investigators and subjects), two-arm, prospective evaluation in healthy adult volunteers. This Phase 1 study evaluated local and systemic safety of iontophoretically-delivered lidocaine and epinephrine administered to the intact tympanic membrane via a non-invasive iontophoretic delivery method.

The study was conducted in accordance with Good Clinical Practices and the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the FDA and the governing Institutional Review Board (IRB: Western IRB, Puyallup, WA). The IRB additionally approved the informed consent forms, and informed consent was received from participants before study conduct. Recruitment, screening, and follow-up visits occurred at the principal investigator's clinic and study procedures including vital sign and blood collection took place at the Worldwide Clinical Trials Early Phase Services facility (San Antonio, TX).

### Subject Population and Inclusion and Exclusion Criteria

Healthy adult volunteers 18 to 50 years of age were candidates for this study. Although children ages 6 months and older are the primary intended target population for tympanostomy tubes, this study was conducted in healthy adults for several reasons. First, it would be inappropriate to conduct the study in children if the evaluation was absent clinical benefit and a suitable alternative was available (3). Second, this pharmacokinetic study involved multiple blood draws that would have been considerably more traumatic and with an increased risk of potential harm in children compared with adults. Third, since iontophoretically facilitated drug is preferentially delivered to the tissue of least electrical resistance (i.e., the TM), healthy adults are appropriate for understanding systemic exposure to drug following iontophoresis in children because the route of entry is the surface of the TM and the TM dimensions achieve full adult size by birth (4). Fourth, iontophoretic delivery of drug dose is linearly proportional to total electrical charge (current integrated over time). The ionic composition of the active and excipient drug ingredients and the physicochemical properties of the drug ingredients play a role in determining the delivered drug dose. The iontophoresis controller firmware is designed to monitor and deliver the same electrical charge and since the physicochemical properties of the drug are well

controlled the actual delivered dose is similar for all subjects. Fifth, even though some characteristics such as plasma volume may differ between children and adults, the literature indicates that lidocaine and epinephrine pharmacokinetic parameters are not materially different between adults and children greater than 6 months of age (5–8). Comparison of weight-normalized pharmacokinetic parameters for lidocaine between adults and children failed to show statistically significant differences (5). As a result, one can extrapolate the lidocaine concentrations in children from the lidocaine concentrations observed in adults based on weight. Therefore, healthy adult subjects were used to adequately understand systemic exposure from topical lidocaine and epinephrine delivery and prevent exposing children to the risks of repeated blood draws, an unapproved drug, and absence of therapeutic benefit. Although ears with acute or chronic otitis media have been shown to have a thicker TM compared with healthy ears (9–10), the iontophoresis control unit will maintain a constant current and adjust the voltage based on tissue resistance. Therefore, the current dose, and therefore ions (drug) delivered, should be the same for TMs of different thicknesses. For these reasons, healthy volunteers, as opposed to those requiring tympanostomy, were acceptable because the systemic exposure was expected to be no different compared with subjects requiring tubes.

Participants were required to have normal hearing thresholds and have healthy ear canals and tympanic membranes, to be in good health, have normal body mass index (BMI), normal resting vital sign measurements, and agree to dietary, medication, nicotine, alcohol product, and physical activity restrictions.

Pregnant or lactating women were excluded from the study as were patients with clinically significant medical illness, history of sensitivity or allergic reaction to lidocaine, tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, had donated or planned to donate blood 3 months before or following the study, had a history of tobacco or nicotine use or drug or alcohol abuse, had electrically sensitive medical support systems or took medications or consumed foods that could interfere with the evaluation of anesthesia or drug levels. Cerumen impaction resulting in a significant amount of cleaning required to visualize the tympanic membrane was exclusionary, as was ear surgery or TM condition with the potential to affect TM sensitivity.

### Iontophoresis System (IPS) and Study Drug Formulations

The IPS (Tula<sup>®</sup> Iontophoresis System, Tusker Medical Inc, Menlo Park, CA) is a single use device, consisting of three components: a control unit, an earset with earplug, and a return electrode. The iontophoresis system includes an integrated fill system. A syringe containing the drug solution is connected to the system tubing via a luer connector. The tubing connects to the earplug lumen which culminates with a soft fill-tip allowing drug solution to be applied directly to the ear canal and TM surface, with the earplug securely in place. Proper instillation was confirmed by the surgeon through visualization of drug filling a clear reservoir lateral to the earplug.

There are several novel aspects of this system that improve the ability to anesthetize the TM in awake, unsedated children in the absence of mechanical restraints, with built in safety controls compared with historical otic iontophoresis systems. During iontophoresis, the adhesive-coated earplug maintains the drug solution in contact with the TM while allowing patient mobility (e.g., eating, playing, watching videos, etc.). The IPS

employs a low-level electric current to transport the ionic drug into the TM tissue. The electrode is embedded within the earplug to prevent direct electrode contact with the patient to minimize discomfort. The IPS is battery-powered and delivers a maximum current of 0.8 mA, with a total charge delivery (dose) of 6.36 mA.minutes. The system controls current delivery and tracks accumulated charge, and is programmed to deliver the same dose of current to all patients and additionally includes features to enhance patient comfort (automatic ramping up and down). As was conducted in this study, iontophoresis may be performed bilaterally, simultaneously for both ears, and the entire nominal iontophoresis program takes approximately 10 minutes.

The lidocaine-based drug formulations evaluated in this study were 2% lidocaine hydrochloride, 1:100,000 epinephrine (TYMBION™, Tusker Medical, Menlo Park, CA) and 2% lidocaine hydrochloride (Hospira, Lake Forest, IL), as the comparator. The lidocaine formulation provides the anesthetic effect, and epinephrine vasoconstricts the local vasculature with the aim to reduce lidocaine clearance away from the target tissue into systemic circulation, thereby increasing the duration of local anesthesia.

Endogenous plasma epinephrine is well known to vary significantly between individuals and may increase greatly (four- to eight-fold or more) during exercise or stress (11–13). Observed plasma epinephrine levels in this study could reflect changes in endogenous epinephrine resulting from the stress associated with the study procedure (e.g., repeated blood collection) or from the exogenous epinephrine administered via iontophoretic delivery. Therefore, a control group (lidocaine alone) was included in this study to aid in interpretation of the measured epinephrine levels. In addition, the control group may illuminate whether the iontophoretically-delivered epinephrine affects the rate of lidocaine absorption away from the local tissue into systemic circulation, by permitting a comparison of the kinetics of systemic lidocaine levels in the presence and absence of administered epinephrine.

**Subject Screening, Randomization, Treatment, and Follow-up**

Screening took place up to 28 days before procedure and included medical history, previous and concomitant medications, cranial nerve examination, otoscopy, tympanometry, audiometry, and vital signs (blood pressure, heart rate, respiratory rate, and pulse oximetry). Subjects were randomized 3:2 on the day of procedure after determining eligibility, where three subjects were assigned to iontophoresis with 2% lidocaine, 1:100:000 epinephrine for every two subjects assigned to iontophoresis with 2% lidocaine alone. An unblinded study staff participant documented the randomization assignment and

prepared the drug solution for the given subject’s procedure by filling a syringe with the allocated drug to enable the subjects and the investigator to be blinded to treatment assignment. Subjects underwent bilateral iontophoresis with the assigned lidocaine-based drug. Effectiveness of anesthesia has been reported for pediatric and adult patients undergoing tube placement in other reports and was not evaluated in this study (14,15). No actual myringotomy with tube placement was performed for the healthy volunteers. All treated subjects were required to complete a follow-up visit 3 days post-procedure to assess safety. Subjects were required to return for a 12-day visit only if the subject had a device-, procedure- or drug-related adverse event that was not resolved by the 3-day visit or per investigator’s decision.

**Pharmacokinetic Analyses**

Blood samples were collected the day of procedure before iontophoresis, immediately post iontophoresis, and thereafter at 5, 15, 25, 35, 50, 80, 110, 170, and 230 minutes. Lidocaine and epinephrine concentration were measured from blood plasma by liquid chromatography with tandem mass spectrometry (LC-MS-MS) method validated for lidocaine (range, 0.200–200 ng/ml) and epinephrine (range, 20.0–4000 pg/ml) (Worldwide Clinical Trial Bioanalytical Services, Austin, TX).

The bioanalytical results were subject to pharmacokinetic analysis (Duck Flats Pharma, LLC, Elbridge, NY) and presented using nominal time point identifiers from start of administration in which the pre-iontophoresis blood sample was considered time 0, immediately post-iontophoresis was considered 11 minutes after iontophoresis start (nominal duration of iontophoresis is 10 min), and subsequent blood sample collections were 15, 25, 35, 45, 60, 90, 120, 180, and 240 minutes after the start of iontophoresis. Table 1 shows the approximate alignment of time intervals based on either start or stop of iontophoresis.

All pharmacokinetic parameters were analyzed using non-compartmental analysis. The program was a validated Phoenix WinNonlin, program (Certara Company, Princeton, NJ), version 7.0. Actual sampling times were used to calculate PK parameters, except for pre-dose samples, which were reported as time zero, regardless of time deviations. The following pharmacokinetic parameters were summarized for both lidocaine and epinephrine at each time point using descriptive statistics: number of observations, arithmetic mean concentration, standard deviation, minimum, median, maximum, and coefficient of variation (CV%). Geometric mean and geometric coefficient of variation were calculated for continuous pharmacokinetic variables. The linear trapezoidal method was used to integrate the plasma concentration versus time profiles out to the time the last measurable concentration was observed. The

**TABLE 1.** Blood plasma sample labeling conventions

Nominal Time Points— Nomenclature	Pre-Dose		Post-Dose									
	Pre- iontophoresis	Immediately post- iontophoresis	5 min	15 min	25 min	35 min	50 min	80 min	110 min	170 min	230 min	
Blood collection (protocol) —time after iontophoresis stop												
Plasma PK analysis (PK report) —time after iontophoresis start	0 min	11 min	15 min	25 min	35 min	45 min	60 min	90 min	120 min	180 min	240 min	

area under the plasma concentration–time curve, from start of iontophoresis to last measurable concentration ( $AUC_{0-last}$ ) was determined by the linear trapezoidal rule. The maximum plasma concentration ( $C_{max}$ ) was determined directly by inspection of the plasma concentration–time curves.

### Safety Evaluations

The primary safety endpoint was the occurrence of adverse events. Safety was analyzed via otologic examination, cranial nerve physical examination, tympanometry, and audiometry at the screening and follow-up visit(s). Otoscopy with binocular microscopy was additionally performed immediately before and following iontophoresis. In addition, vital sign assessments (diastolic and systolic blood pressure, blood oxygen saturation, respiration, and heart rates) were taken 15 minutes previous and immediately before iontophoresis, immediately after iontophoresis, 6, 12, 18, 24, 30, 60, 90, and 120 minutes post-iontophoresis. The greater of the two pre-iontophoresis measurements was used as the baseline measure for the analysis of mean change from baseline. Vital sign normal ranges were defined as systolic blood pressure 90 to 140 mmHg, diastolic blood pressure 50 to 90 mmHg, pulse rate 45 to 100 beats/min, respiration rate 8 to 20 breaths/min, and blood oxygen saturation 97 to 100%.

### Sample Size and Statistical Analysis

The subject sample size was chosen based on variability in resting endogenous epinephrine and measured lidocaine plasma concentrations reported in published studies (11,16). This pharmacokinetic study included 15 subjects in the treatment arm (2% lidocaine, 1:100,000 epinephrine) and 10 subjects in the comparator arm (2% lidocaine only). With a sample size of 12 treatment and eight control subjects, the study was designed to detect a doubling of epinephrine levels (assuming a constant % coefficient of variation, CV) at  $\alpha = 0.025$  with a power of approximately 80%. A sample size of 12 subjects allowed an estimated 90% confidence interval for the mean  $C_{max}$  (maximum plasma concentration) of lidocaine value to be in the range of the mean  $\pm 14\%$ , assuming a similar coefficient of variation (31% CV) for lidocaine as in Leopold et al. (16), who described pharmacokinetics of lidocaine concentrations resulting from a transmucosal patch in children. To account for uncertainty in plasma lidocaine and epinephrine drug level variability, a total sample size of 15 subjects in the treatment arm and 10 subjects in the control arm was selected. Data analyses include descriptive and summary statistics.

## RESULTS

### Patient Demographics and Disposition

Thirty-one (31) healthy adult volunteers were enrolled (consented) in the study. Twenty-five of the participants were randomized and treated. Five subjects did not meet eligibility criteria and one subject was eligible but was not randomized or treated due to completion of enrollment of the targeted 25 subjects. The treated study population was comprised of six women (24%) and 19 men (76%), with a mean (standard deviation, SD) age of 27.2 (7.8) years. The proportion of men in each group was similar with 80% men in the lidocaine with epinephrine group and 70% men in the lidocaine alone group. All 25 subjects and 50/50 (100%) ears completed simultaneous bilateral iontophoresis. Blood samples were collected from all randomized

subjects for analysis of plasma lidocaine and epinephrine levels. All 25 treated subjects completed the required 3-day follow-up visit and exited the study as there were no device-, procedure-, or drug-related adverse events that were unresolved at the 3-day follow-up visits requiring additional follow-up.

### Safety

There were no device-, procedure-, or drug-related adverse events. There were no observed clinically significant changes in vital sign measurements, otoscopy, tympanometry, audiometry, or cranial nerve examination. As shown in Table 2, subjects in both groups demonstrated minor insignificant changes in mean vital sign measurements post-iontophoresis compared with baseline. Two (2) subjects experienced transient vasovagal syncope during intravenous cannula insertion before the iontophoresis procedure.

### Pharmacokinetic Assessment

The plasma lidocaine concentration–time curve resulting after the administration of lidocaine with epinephrine was compared with that of the comparator formulation consisting of lidocaine alone. Mean plasma concentrations of lidocaine were not statistically different between groups, ranging from 0.245 to 2.28 ng/ml after administration of lidocaine with epinephrine (immediate post-iontophoresis to 230 min post-iontophoresis), compared with 1.35 to 2.14 ng/ml after administration of lidocaine alone, shown in Table 3 and Figure 1. In the presence of epinephrine, the systemic absorption of lidocaine during iontophoresis appeared to be suppressed, as indicated by the lower mean lidocaine concentrations at the initial post-iontophoresis time points (0.245 ng/ml compared with 1.35 ng/ml for the lidocaine with epinephrine and lidocaine alone formulations, respectively). Although the rate at which the mean plasma lidocaine concentrations increased began to plateau over the 4-hour observation period, the declining portion of the pharmacokinetic curve was not captured. No statistical difference in the geometric means of either lidocaine  $C_{max}$  or  $AUC_{0-last}$  (area under the plasma concentration–time curve, from start of iontophoresis to last measurable concentration) was shown when comparing the treatment formulation to that of the comparator ( $C_{max}$  2.25 and 1.98 ng/ml, and  $AUC_{0-last}$  337 and 334 min ng/ml, respectively). Measured  $C_{max}$  lidocaine concentrations for both lidocaine with epinephrine and lidocaine alone arms were approximately 2000-fold lower than the reported threshold for minor lidocaine toxicity of 6  $\mu\text{g/ml}$  (17).

The mean plasma epinephrine concentration values fluctuated between 23.1 and 30.8 pg/ml after administration of the lidocaine with epinephrine (minimum and maximum mean concentrations over the time course), compared with 20.5 to 38.1 pg/ml after administration of lidocaine alone (Table 4 and Fig. 2). No statistical difference in the medians, means, or geometric means



**TABLE 2.** Vital sign baseline values and change from baseline

Formulation	Measurement	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse Rate (beats/min)	Respiratory Rate (breaths /min)	Oxygen Saturation (%)
		Mean (SD) (N)				
2% Lidocaine/ 1:100,000 Epinephrine	Baseline measurements:					
	15 minutes pre-ionto	124.1 (13.5) (15)	73.3 (8.5) (15)	71.5 (10.3) (15)	14.1 (2.7) (14)	99.3 (1.3) (14)
	0 minute pre-ionto	123.1 (12.2) (15)	74.7 (10.5) (15)	70.3 (10.7) (15)	14.3 (2.6) (15)	98.9 (1.4) (15)
	Change from higher baseline:					
	Immediately post-ionto	-3.9 (5.9) (15)	-4.5 (6.3) (15)	-4.0 (4.6) (15)	0.0 (2.7) (15)	-1.1 (1.2) (15)
	6 minutes post-ionto	-6.5 (7.1) (15)	-5.4 (7.1) (15)	-2.8 (6.2) (15)	-0.7 (2.4) (15)	-0.3 (1.0) (15)
	12 minutes post-ionto	-5.9 (9.2) (15)	-2.7 (4.6) (15)	-3.1 (2.7) (15)	-1.5 (3.2) (15)	-0.8 (1.5) (15)
	18 minutes post-ionto	-5.4 (9.3) (13)	-6.3 (5.2) (13)	-1.5 (6.6) (13)	-0.9 (2.7) (13)	-0.4 (0.8) (13)
	24 minutes post-ionto	-6.2 (7.3) (15)	-5.7 (5.4) (15)	-2.1 (4.0) (15)	-0.4 (2.2) (15)	-0.7 (1.0) (15)
	30 minutes post-ionto	-7.5 (9.9) (15)	-4.7 (6.1) (15)	-0.6 (4.5) (15)	-1.1 (3.0) (15)	-0.3 (0.8) (15)
	60 minutes post-ionto	-6.1 (8.7) (15)	3.9 (8.5) (15)	-5.7 (4.9) (15)	-1.2 (2.8) (15)	0.2 (1.2) (15)
	90 minutes post-ionto	-8.7 (6.0) (15)	-5.5 (5.9) (15)	-6.6 (8.5) (15)	-0.8 (2.6) (15)	0.0 (1.2) (15)
	120 minutes post-ionto	-9.8 (5.7) (15)	-7.3 (7.3) (15)	-5.8 (5.5) (15)	-1.5 (2.8) (15)	0.0 (1.1) (15)
2% Lidocaine	Baseline measurements:					
	15 minutes pre-ionto	124.9 (8.7) (10)	73.8 (8.1) (10)	71.4 (13.8) (10)	12.0 (3.0) (9)	99.0 (1.3) (9)
	0 minute pre-ionto	123.6 (10.7) (10)	72.9 (7.9) (10)	73.6 (14.1) (10)	15.0 (2.9) (10)	98.7 (1.3) (10)
	Change from higher baseline:					
	Immediately post-ionto	-3.2 (7.7) (10)	-1.7 (5.9) (10)	-9.8 (9.1) (10)	-0.4 (1.6) (10)	-0.5 (0.7) (10)
	6 minutes post-ionto	-7.6 (6.8) (10)	-3.0 (7.3) (10)	-6.9 (8.6) (10)	-0.6 (1.9) (10)	-0.9 (2.0) (10)
	12 minutes post-ionto	-9.9 (10.2) (10)	-1.5 (4.9) (10)	-5.4 (8.9) (10)	-0.2 (3.2) (10)	-1.0 (0.9) (10)
	18 minutes post-ionto	-9.1 (5.8) (10)	-3.1 (5.7) (10)	-7.4 (7.2) (10)	0.4 (2.3) (10)	-0.6 (1.5) (10)
	24 minutes post-ionto	-7.6 (9.3) (10)	-3.5 (4.8) (10)	-6.4 (6.3) (10)	-0.8 (3.9) (10)	-1.0 (1.1) (10)
	30 minutes post-ionto	-11.8 (6.8) (10)	-3.2 (6.6) (10)	-6.5 (6.8) (10)	-0.8 (3.7) (10)	-1.1 (1.0) (10)
	60 minutes post-ionto	-13.7 (5.4) (10)	-7.0 (8.3) (10)	-9.3 (6.8) (10)	-1.4 (3.1) (10)	0.2 (0.8) (10)
	90 minutes post-ionto	-8.2 (8.3) (10)	-7.8 (8.5) (10)	-9.8 (5.3) (10)	-1.2 (3.2) (10)	0.1 (0.7) (10)
	120 minutes post-ionto	-11.7 (4.8) (10)	-6.8 (8.6) (10)	-11.0 (6.3) (10)	-1.0 (3.8) (10)	-0.1 (1.0) (10)

**TABLE 3.** Comparative lidocaine concentrations

Formulation	Statistic	Lidocaine										
		Nominal Time Post Start of Iontophoresis (min)										
		0 <sup>a</sup>	11 <sup>b</sup>	15	25	35	45	60	90	120	180	240
2% Lidocaine/1:100,000 Epinephrine	N	15	15	15	15	15	14	15	15	15	15	15
	Mean	0	0.245	0.395	0.579	0.755	0.869	0.966	1.26	1.64	2.20	2.28
	SD	0	0.317	0.386	0.416	0.452	0.437	0.444	0.545	0.807	0.896	0.762
	Min	0	0	0	0	0	0	0.329	0.354	0.665	1.01	1.19
	Median	0	0	0.326	0.565	0.722	0.915	0.975	1.31	1.42	1.97	2.11
	Max	0	0.881	1.39	1.29	1.46	1.65	2.17	2.48	3.52	3.77	3.64
	CV%	-	129	97.8	71.9	59.9	50.3	46.0	43.3	49.2	40.7	33.4
	Geo Mean	NC	NC	NC	NC	NC	NC	0.875	1.14	1.48	2.04	2.16
	CV% Geo Mean	NC	NC	NC	NC	NC	NC	50.1	51.8	49.2	43.3	34.9
2% Lidocaine	N	10	10	10	10	10	10	10	10	10	10	10
	Mean	0	1.35	1.38	1.38	1.30	1.36	1.34	1.62	1.77	2.09	2.14
	SD	0	1.34	1.17	1.11	1.04	1.24	1.21	1.70	1.71	1.61	1.48
	Min	0	0	0.269	0.485	0.511	0.523	0.592	0.702	0.808	0.989	1.12
	Median	0	0.983	1.05	0.982	0.841	0.834	0.840	0.945	1.11	1.39	1.56
	Max	0	4.54	4.00	4.04	3.89	4.61	4.49	6.15	6.33	6.20	5.85
	CV%	-	99.8	85.2	80.4	80.1	91.1	90.5	105	96.6	77.1	69.3
	Geo Mean	NC	NC	0.975	1.08	1.04	1.06	1.05	1.20	1.37	1.74	1.83
	CV% Geo Mean	NC	NC	112	82.0	73.2	77.1	75.1	81.2	73.3	63.9	58.3

<sup>a</sup>Time 0 minutes, pre-iontophoresis.

<sup>b</sup>Time 11 minutes, immediately post-iontophoresis.

CV% Geo Mean indicates percent coefficient of variation of the geometric mean; CV%, percent coefficient of variation; Geo Mean, geometric mean; Max, maximum; Min, minimum; NC, not calculated; SD, standard deviation.

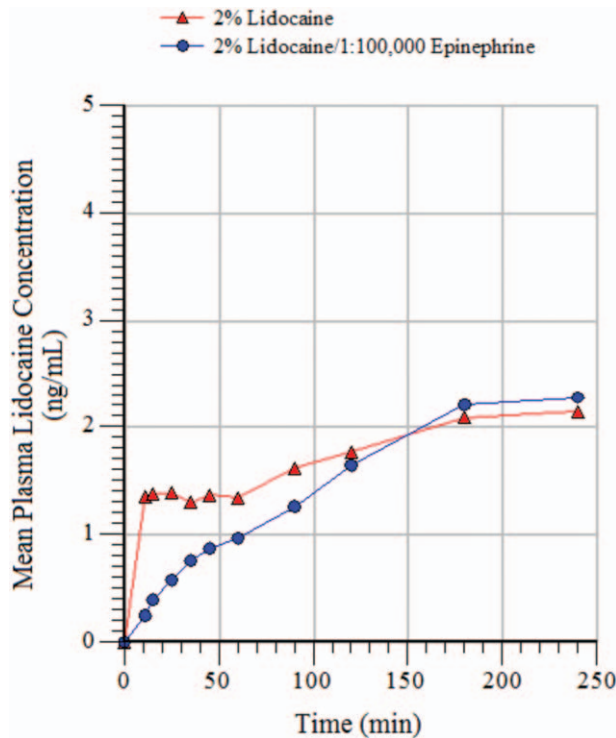


FIG. 1. Mean lidocaine plasma levels.

of either  $C_{max}$  or  $AUC_{0-last}$  was observed when comparing the treatment to that of the comparator (lidocaine alone with endogenous epinephrine only) formulations ( $C_{max}$  39.9 and 43.6 pg/ml, and  $AUC_{0-last}$  5160 and

3850 min pg/ml, respectively). There was no significant elevation of the circulating endogenous epinephrine hormone. Measured epinephrine concentrations for both the lidocaine with epinephrine and the lidocaine alone comparator arms were within the reported normal range for endogenous epinephrine (30–50 pg/ml) (11,12). After administration of either formulation, a trend was detected in that lower circulating epinephrine levels were observed after the initiation of the otic procedure as compared with baseline pre-dose levels. This may be a result of subjects' initial apprehension of the study procedures, potentially resulting in stress-induced increases in epinephrine, which dissipated shortly after the start of the clinical dosing.

DISCUSSION

This study describes the local and systemic safety profile of 2% lidocaine, 1:100,000 epinephrine local anesthetic administered bilaterally to the tympanic membrane using the iontophoresis system. The ability to safely provide local anesthetic to the tympanic membrane is critical to enabling tympanostomy tube placement in pediatric patients in an office setting and avoid the risks, stresses, and inconveniences associated with general anesthesia including the potential for neurodevelopmental effects of repeated or lengthy general anesthesia exposure (18–20), and common pediatric preoperative anxiety and postoperative stress behaviors (21–24).

Tympanostomy tube placement is commonly performed for adults and older children in an office setting using local anesthetics such as phenol (carbolic acid), EMLA cream (Eutectic Mixture of Local Anesthetics,

TABLE 4. Comparative epinephrine concentrations

Formulation	Statistic	Epinephrine										
		Nominal Time Post Start of Iontophoresis (min)										
		0	11	15	25	35	45	60	90	120	180	240
2% Lidocaine/1:100,000 Epinephrine	N	14	13	12	11	11	10	13	12	11	11	11
	Mean	30.2	26.3	28.4	28.2	28.9	30.0	28.7	23.1	25.0	28.5	30.8
	SD	20.0	15.9	12.4	17.5	17.4	13.3	14.6	13.1	11.0	8.04	10.1
	Min	0	0	0	0	0	0	0	0	0	20.2	21.5
	Median	32.2	22.9	27.6	29.2	29.1	30.2	25.7	22.5	23.5	27.6	28.4
	Max	64.7	58.9	48.1	53.4	49.1	47.8	61.1	40.3	41.9	47.2	49.1
	CV%	66.3	60.4	43.6	62.0	60.2	44.3	50.9	56.6	43.9	28.2	32.9
	Geo Mean	NC	NC	NC	NC	NC	NC	NC	NC	NC	27.6	29.5
2% Lidocaine	N	10	9	9	9	9	8	5	4	5	6	5
	Mean	38.1	21.7	24.3	28.6	27.9	31.6	23.8	20.5	22.0	35.0	33.0
	SD	33.2	22.8	21.1	23.4	16.8	16.1	14.9	14.4	13.1	11.5	8.40
	Min	0	0	0	0	0	0	0	0	0	20.4	22.7
	Median	25.8	29.6	28.4	37.3	37.0	33.6	23.3	25.5	27.5	36.5	33.9
	Max	97.9	61.9	58.2	58.4	43.5	54.8	36.9	30.9	32.8	48.6	44.5
	CV%	87.0	105	86.7	81.9	60.2	50.8	62.7	70.2	59.6	33.0	25.4
	Geo Mean	NC	NC	NC	NC	NC	NC	NC	NC	NC	33.3	32.2
CV% Geo Mean	NC	NC	NC	NC	NC	NC	NC	NC	NC	37.1	26.5	

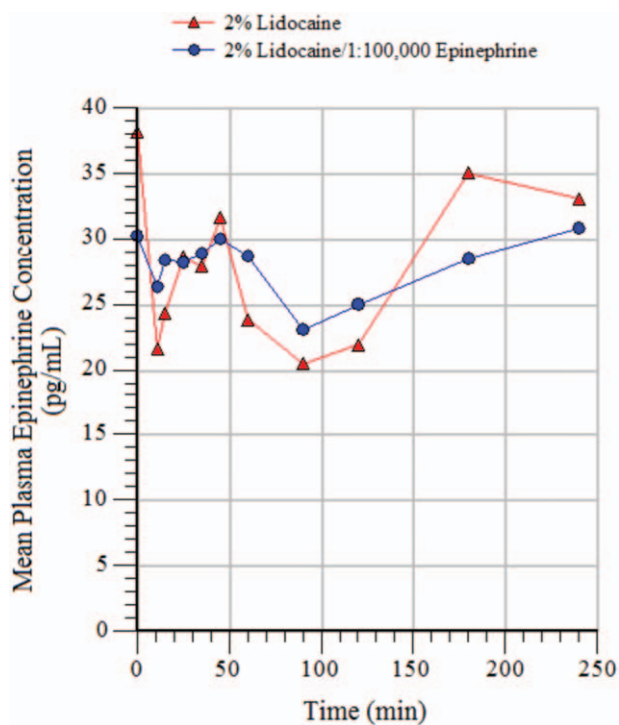


FIG. 2. Mean epinephrine plasma levels.

lidocaine 2.5% and prilocaine 2.5%), lidocaine HCl injections, Bonain's solution (cocaine hydrochloride, menthol, phenol), or tetracaine injections (25–28). None of these anesthetics are indicated for anesthesia of the ear drum, and none are commonly used for small children due to discomfort associated with their use, the duration of time required to achieve anesthesia or concerns of ototoxicity if drug should enter the middle ear (26,29).

Numerous reports from the 1970s to 1980s described otic iontophoresis using different technologies and drug formulations (30–46). This body of work provided important preliminary data on safety (cochlear responses and side effects) of iontophoretic administration of lidocaine and epinephrine to the tympanic membrane, however none reported on systemic exposure resulting from iontophoretic drug delivery. Given the target population for lidocaine iontophoresis and tympanostomy tube placement is very young children, this evaluation aimed to provide definitive pharmacokinetic data using modern, validated, and highly-sensitive methods for the current, commercially available system and drug formulation.

While lidocaine can be administered systemically as a therapeutic antiarrhythmic in the range of 1.5 to 5  $\mu\text{g}/\text{ml}$ , levels greater than 6  $\mu\text{g}/\text{ml}$  can result in systemic side effects such as drowsiness, tinnitus, dysgeusia, dizziness, and twitching (17). Peak ( $C_{\text{max}}$ ) blood levels of lidocaine measured in the current pharmacokinetic study were less than 2.24 ng/ml which is 2000-fold lower than a concentration that would be expected to cause systemic toxicity. To extrapolate to children of the youngest indicated age (assume a 5.9 kg 6-month-old female), assuming all drug

in the ear canal was delivered bilaterally (1.7 ml, 27.54 mg lidocaine) and was 100% bioavailable, instantaneous absorption, and a volume of distribution for the central compartment ( $V_1$ ) of 0.22 L/kg (5), the theoretical worst-case maximum plasma concentration of lidocaine is 21.22  $\mu\text{g}/\text{ml}$ , exceeding the threshold of minor toxicity (6  $\mu\text{g}/\text{ml}$ ). For a 5.9 kg child, this calculated maximum exposure is approximately 12-fold higher than for a 70 kg adult man. Therefore, it is relevant to have established that the actual measured systemic exposure in adults was several orders of magnitude lower (2000-fold) than the threshold for minor toxicity, providing assurance that the systemic exposure in children would accordingly be approximately 200-fold lower than this threshold. It was anticipated that observed plasma levels would be low because, although approximately 1.7 ml of the lidocaine and epinephrine solution is administered bilaterally into the ear canals, it is expected that only a small fraction of drug in that volume is actually delivered across the epidermal barrier into the tissue.

Lidocaine has vasodilatory properties that can accelerate local clearance from the target anesthetic zone. Epinephrine is a potent vasoconstrictor that can offset lidocaine's vasodilatory tendencies and thus prolong the tissue concentration of lidocaine and duration of local anesthesia. Endogenous plasma epinephrine concentrations in resting healthy adults are normally 30 to 45 pg/ml but can vary significantly between individuals and may increase greatly (4- to 8-fold or more) during exercise or stress (11–13). In all subjects at all time points, epinephrine blood concentrations remained within normal endogenous levels.

A limitation of the study was evaluation of post-iontophoresis plasma lidocaine and epinephrine levels in healthy adult ears, whereas the predominant target population for this therapy is children with otitis media. TM tissue properties between adults and children are similar. Both pediatric and adult ears with otitis media have been shown to have thicker TMs compared with healthy ears. However, the iontophoresis control unit will maintain a constant current and adjust voltage based on tissue resistance. Therefore, the current dose, and therefore ions (drug) delivered should be the same for healthy ears and ears with otitis media. Other differences, such as presence of effusion or increased vascularization, may play a role in the time course of systemic absorption. However, given the extremely low levels detected systemically, the inability to fully simulate the clinically-relevant tissue is thought to not materially alter the conclusions. A second limitation of the study was the inability to determine the  $\text{AUC}_{0-\infty}$  (area under the plasma concentration–time curve from start of iontophoresis to infinity), as the terminal exponential portion for the individual subject pharmacokinetic curves could not be identified. The lack of a complete pharmacokinetic curve is immaterial to the safety conclusions of the study, as the systemic lidocaine concentration was well below the safety threshold for minor toxicity (17). An additional limitation to the study is absence of balance by sex. While young women

may have increased metabolism of lidocaine compared with men due to greater CYP3A4 activity (47), the inclusion of a larger proportion of men in each arm (80% in the lidocaine with epinephrine group and 70% in the lidocaine alone group) would potentially result in higher observed plasma lidocaine levels representing worst-case given the lack of detection above endogenous epinephrine levels, the lack of sex balance is unlikely to materially alter conclusions.

This study demonstrated safety of bilateral iontophoretic delivery of 2% lidocaine, 1:100,000 epinephrine to the tympanic membrane supported by low plasma levels of drug, and absence of both serious and non-serious device-, procedure-, or drug-related adverse events. There was no statistical difference in plasma epinephrine levels between control subjects (no applied epinephrine) and subjects who underwent iontophoresis with the lidocaine solution containing epinephrine, and levels were comparable to reported endogenous epinephrine for both treatment groups. Lidocaine levels were shown to be low, approximately 2000-fold lower than levels associated with toxicity. Overall study results indicate a favorable safety profile which supported initiation of clinical investigations of iontophoretically-administered 2% lidocaine, 1:100,000 epinephrine, and automated tympanostomy tube delivery in the pediatric population (15). This method of iontophoretically-facilitated anesthesia using the iontophoresis system with 2% lidocaine, 1:100,000 epinephrine was recently FDA approved for use in children (aged 6 mos and older) and adults undergoing tympanostomy tube placement, in a physician's office setting.

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